Incremental Prognostic Value of Regurgitant Fraction in Patients with Ventricular Secondary Mitral Regurgitation

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Article

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Abstract

Objectives: Quantifying ventricular secondary mitral regurgitation (MR) remains challenging, and the prognostic value of echocardiographic parameters is uncertain. This study aimed to assess the concordance of parameters of MR severity and determine the added value of regurgitant fraction (RF) in predicting outcomes. **Methods and results:** We retrospectively analysed 186 patients with ventricular secondary MR who underwent echocardiography with MR assessment, evaluating effective regurgitant orifice area (EROA), regurgitant volume (RegVol) and RF. The primary endpoint was a composite of all-cause death or heart failure hospitalisation. Quantitative parameters of MR severity were frequently discordant. Using the guideline-recommended cut-offs for EROA (≥ 40 mm^2), RegVol (≥ 60 ml) and RF (≥ 50%), severe MR was present in 5.4%, 3.3%, and 29.5% of patients, respectively. Both RF ≥ 50% and EROA ≥ 40 mm^2 were independently associated with clinical outcomes in multivariable Cox models. Combining RF and EROA provided incremental prognostic value over either parameter alone ($p < 0.05$). Kaplan-Meier curves showed that patients with EROA < 40 mm^2 and RF ≥ 50% had similar outcomes to those with EROA ≥ 40 mm^2 ($p = 0.055$), whereas patients with both EROA < 40 mm^2 and RF < 50% had significantly better outcomes ($p = 0.002$). **Conclusions:** Substantial discordance between quantitative parameters of severe MR was observed in ventricular secondary MR. RF is a strong, underutilised marker of MR severity, reflecting haemodynamic burden beyond EROA and RegVol. Patients with EROA < 40 mm^2 and RF > 50% had outcomes comparable to those who met guideline-based threshold for severe MR, defined as EROA ≥ 40 mm^2. Our results demonstrate that routine RF assessment enhances risk stratification and enables identification of a high-risk subgroup of patients with EROA < 40 mm^2.

Keywords: mitral regurgitation; quantification; PISA method; regurgitant fraction; outcome

1. Introduction

Accurate quantification of the severity of ventricular secondary mitral regurgitation (MR) is essential for risk stratification and clinical decision-making regarding the timing of interventions. Several parameters have been described for quantifying MR, including effective regurgitant orifice area (EROA), regurgitant volume (RegVol) and regurgitant fraction (RF). Previous studies have demonstrated the prognostic value of EROA in patients with secondary MR [1–5]. These studies have shown that the risk of all-cause death and/or heart failure hospitalisation increases above certain thresholds, ranging from 6 to 30 mm^2. These diverging thresholds introduce uncertainty regarding a uniform cut-off value for EROA across the entire spectrum of patients with secondary MR. As shown in theoretical paper, EROA and RegVol values associated with severe secondary MR depend not only on haemodynamic status, but also on left ventricular (LV) size and ejection fraction [6]. Therefore,

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defining the magnitude of valve dysfunction purely based on lesion severity assessment by EROA or RegVol might be problematic, as using uniform cut-offs could lead to underestimation of the haemodynamic significance of valve lesion in specific patient groups.

Conversely, RF which was rarely analysed in previous publications, provides a size-independent measure of MR severity and defines volume overload of the valve lesion. An RF greater than 50% appears to be a reasonable cut-off for defining haemodynamic significance, as more than half of the total LV stroke volume is lost backward into the left atrium. RF might provide better definition for haemodynamic significance of MR than EROA or RegVol, as it already accounts for low flow conditions. There are limited data suggesting that using RF improves risk stratification of patients with secondary MR [7], but further research is needed to confirm this.

Accordingly, the aim of our study was to (1) evaluate the concordance of quantitative parameters of MR severity, (2) assess the prognostic value of individual quantitative parameters of MR severity, and (3) determine the added value of RF over traditional quantitative parameters in patients with ventricular secondary MR.

2. Materials and Methods

2.1. Study Population

A retrospective study was conducted among patients who were referred for clinically indicated echocardiography between January 1 and December 31, 2019, at Department of Cardiology, University Medical Centre Ljubljana. Consecutive patients with at least mild secondary MR using a multiparametric integrative approach and history of LV systolic dysfunction caused by either dilated or ischemic cardiomyopathies, as well as those who had basal inferior myocardial infarction resulting in posterior leaflet tethering were included. Patients with MR, in whom proximal isovelocity surface area (PISA) method for MR quantification could not be performed–such as those with eccentric regurgitant jets, multiple jets, or no visible PISA radius–were excluded. Additional exclusion criteria were more than mild aortic regurgitation, mitral stenosis or previous mitral valve replacement. Echocardiograms were reviewed from echocardiographic database and clinical data were obtained from medical records. The study protocol was approved by the National Medical Ethics Committee.

2.2. Echocardiographic Assessment

Standard 2D and Doppler transthoracic echocardiography was performed using commercial echocardiographic machines (Vivid E9, Vivid S60 (GE Vingmed Ultrasound AS, Horten, Norway), iE33 (Philips Medical Systems, Bothell, WA, USA)). Digitally stored data were retrospectively analysed offline (Echopac, version 20.4, GE Vingmed Ultrasound AS). The standard measurements were performed in accordance with the most recent recommendations [8]. LV volumes and ejection fraction (LVEF) were estimated by the Simpson's biplane method. LV total stroke volume (total SV) was calculated as the difference between LV end-diastolic (LVEDV) and end-systolic volume (LVESV). Forward SV was calculated from the velocity time integral (VTI) of the LV outflow tract measured by the pulsed wave Doppler, multiplied by the LV outflow tract area [9,10]. Conventional parameters for right ventricle (RV) size and function as well as pulmonary artery systolic pressure, were measured according to the recommendations [11]. The following quantitative parameters of MR severity were reported: EROA, RegVol and RF by PISA method (Graphical abstract). EROA and RegVol were calculated by standard PISA approach using a measurement of PISA radius at mid-systole [9,10]. RF was calculated as the percentage of RegVol to total SV.

2.3. Outcome

All patients were followed until the end of 2023. The study outcome was composite of all-cause death or hospitalisation due to heart failure. Patients were censored at the time of mitral valve intervention or at the end of follow-up if they did not experience the event. Follow-up data were

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obtained by retrospective review of hospital medical records and the national health database. Physicians, blinded to echocardiographic data, assigned clinical events.

2.4. Statistical Analysis

Continuous variables were presented as mean ± standard deviation, if normally distributed, otherwise as medians and interquartile ranges. Categorical data were summarised as frequencies and percentages. The unpaired Student t-test or Mann-Whitney test was used to compare two groups. Categorical variables were compared using a chi-square test or Fisher exact test. Associations between parameters of MR severity were assessed using Pearson correlation coefficients, while Cohen's Kappa coefficients evaluated concordance between guideline-recommended cut-offs. Kaplan–Meier curve analysis was performed to estimate event-free survival rates, and log-rank tests were used to assess differences between groups. To assess the pattern of MR severity parameters associated with clinical outcome, a restricted spline curve with four-knots was used, where the x-axis represents MR severity parameters as a continuous variable, and the y-axis represents the unadjusted hazard ratio (HR) for composite endpoint. Univariate and multivariate Cox proportional hazards models were used to assess association with survival, presented as HR with corresponding 95% confidence intervals (CI). Clinically relevant variables and those showing significant association in univariable analyses were entered into multivariate model. A rule of 10 events per variable was applied to prevent overfitting of the multivariate model [12]. Collinearity of variables was tested using the variance inflation factor (considered excessive if > 3) and the variance proportion (considered excessive if > 0.5). LVESV, LVESV index (LVESVi) and LVEF, tricuspid annular plane systolic excursion (TAPSE) and RV diameter, RegVol and EROA were not included together in the multivariate analysis due to strong collinearity. To compare the prognostic value of MR severity parameters, different multivariable models were constructed using the same baseline model. The baseline model was best-fit model using clinical variables and echocardiographic parameters of LV and RV size/function (age, LVESV index, SV index, RV diameter and pulmonary systolic pressure). The predictive accuracy (discriminative ability) of different models was assessed using likelihood ratio tests to evaluate changes in χ^2 values. A two-tailed p-value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 (IBM, Chicago, IL, USA) and R version 4.4.2 (Vienna, Austria).

3. Results

3.1. Study Population

The study cohort included 186 patients with ventricular secondary MR. Of these, 19 (10.2%) patients had MR grade IV based on integrative approach, 14 (7.5%) had grade III, 91 (48.9 %) had grade II, and 62 (33.3%) had grade I. Approximately half of the patients had ischaemic cardiomyopathy and nearly third had atrial fibrillation. Other clinical and echocardiographic data are listed in **Table 1**.

Table 1. Clinical and echocardiographic characteristics of the study population according to the composite clinical endpoint.

	All patients (n=186)	**No events (n= 79)**	**Events (n=107)**	**P-value**
Clinical characteristics				
Age (years)	69±12	65±13	72±10	0.001
Gender (male)	129 (69)	56 (71)	73 (68)	0.697
BMI (kg/m2)	27±5	28±4	27±5	0.299
Systolic blood pressure (mmHg)	122±20	125±19	119±20	0.106
Heart rate (bpm)	77±19	76±22	77±17	0.700
Atrial fibrillation (%)	50 (27)	18 (23)	32 (27)	0.279

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Ischemic cardiomyopathy (%)	101 (54)	41 (52)	60 (56)	0.572
Echocardiographic characteristics				
LVEDD (mm)	62±10	62±9	62±11	0.990
LVESD (mm)	51±12	50±11	51±12	0.414
LVEDV index (ml)	100 (79-124)	95 (77-119)	107 (83-126)	0.109
LVESV index (ml)	64 (44-84)	58 836-76)	69 (49-88)	**0.017**
LVEF (%)	35 (29-45)	41 (32-42)	34 (27-42)	**0.001**
Stroke volume index (ml/m^2)	31±11	33±13	29±8	**0.028**
CO (l/min)	4.2 (3.4-5.0)	4.1 (3.4-5.4)	4.2 (3.2-4.8)	0.199
RV basal diameter (mm)	41±8	39±7	42±8	**0.001**
TAPSE (mm)	18±5	19±5	18±4	**0.009**
PASP (mmHg)	48±13	46±14	50±12	0.068
EROA (mm^2)	19 (14-25)	17 (12-23)	19 (14-25)	0.140
RegVol (ml)	27 (19-37)	26 (20-33)	27 (19-37)	0.640
RF (%)	39 (29-54)	36 (25-46)	40 (30-59)	**0.017**

Legend: BMI-body mass index, EROA-effective regurgitant orifice area, LVEDD-left ventricular end-diastolic diameter, LVEDV- left ventricular end-diastolic volume, LVEF-left ventricular ejection fraction, LVESD-left ventricular end-systolic diameter, LVESV-left ventricular end-systolic volume, MR-mitral regurgitation, PASP-pulmonary artery systolic pressure, RegVol-regurgitant volume, RF-regurgitant fraction, RV-right ventricle, TAPSE- tricuspid annular plane systolic excursion.

3.2. Comparison of Parameters of MR Severity

All quantitative parameters for MR severity correlated well with each other, although not perfectly (EROA vs. RegVol: r = 0.855, p < 0.001; EROA vs. RF: r = 0.586, p < 0.001; RegVol vs. RF: r = 0.584, p < 0.001). The correlation and concordance of the quantitative measurements are shown in **Graphical abstract** and **Figure 1**. Using the guideline-recommended cut-offs for EROA (≥ 40 mm2), RegVol (≥ 60 ml) and RF (≥ 50%), severe MR was present in 10 (5.4%), 6 (3.3%) and 54 (29.5%) patients, respectively. The observed agreement between the recommended cut-offs was 96% for EROA and RegVol, with Kappa coefficient of 0.479 (95% CI 0.172-0.786, p < 0.001). The agreement between the recommended cut-offs was lower for EROA and RF (observed agreement 74%; Kappa coefficient: 0.174 (95% CI 0.051-0.296, p < 0.001)) and for RegVol and RF (observed agreement 73%; Kappa coefficient: 0.114 (95% 0.011-0.218), p < 0.001)). Patients with discordant grading (EROA vs. RF) had smaller LV and lower SV than those with concordant grading (**Table S1**).

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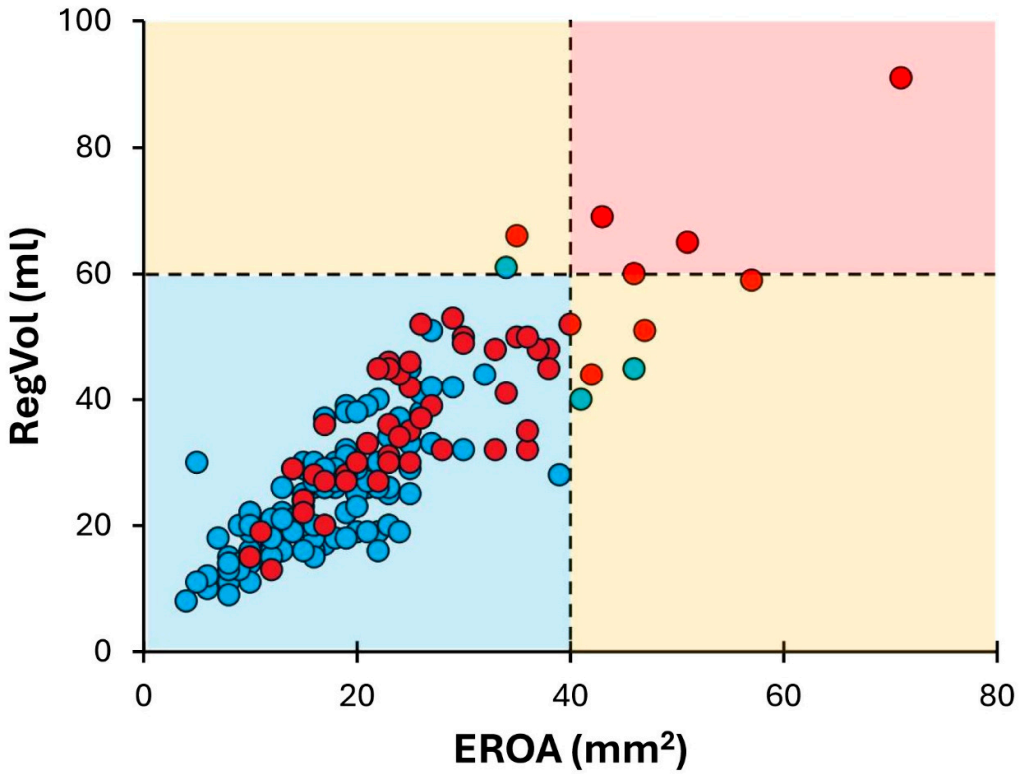

Figure 1. Correlation and concordance among the parameters of MR severity. EROA and RegVol correlated well with each other (r = 0.855, p < 0.001). The red box indicates patients with concordant severe MR, and the blue box indicates patients with concordant non-severe MR while yellow boxes represent patients with discordant MR severity, when using the recommended cut-offs: EROA (≥ 40mm²) or RegVol (≥ 60 ml). Red dots represent patients with RF ≥ 50%, while blue dots represent patients with RF < 50%. A substantial number of patients with RF > 50% (red dots), were classified as non-severe MR according to EROA or RegVol cut-offs (blue box). Abbreviations as in Graphical abstract.

3.3. Association of MR Severity with Clinical Outcomes

During a median follow-up of 769 (106-1584) days, 107 patients reached composite endpoint (50 deaths and 57 hospitalisations due to heart failure). Approximately 7% (13) of patients underwent mitral valve interventions. Patients who reached composite endpoint were older and had more pronounced LV and RV remodelling, as well as more impaired systolic function (**Table 1**). Regarding the quantitative parameters of MR severity, patients with clinical events had higher RF, while EROA and RegVol were comparable.

Kaplan-Meier analysis for composite clinical outcome showed that the recommended cut-off values for EROA and RF significantly discriminated cumulative survival between patients with severe and non-severe MR, while no significant differences were observed in survival when assessing severity with RegVol (**Figure 2**).

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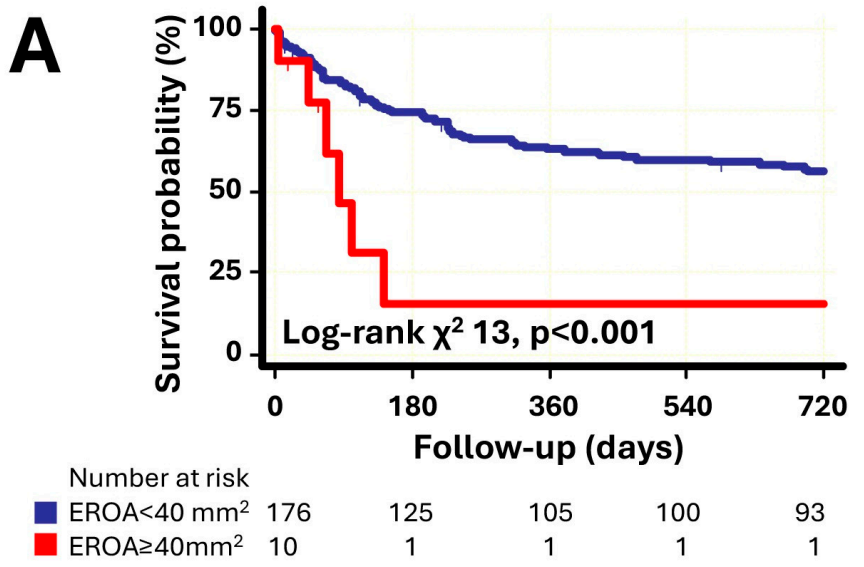

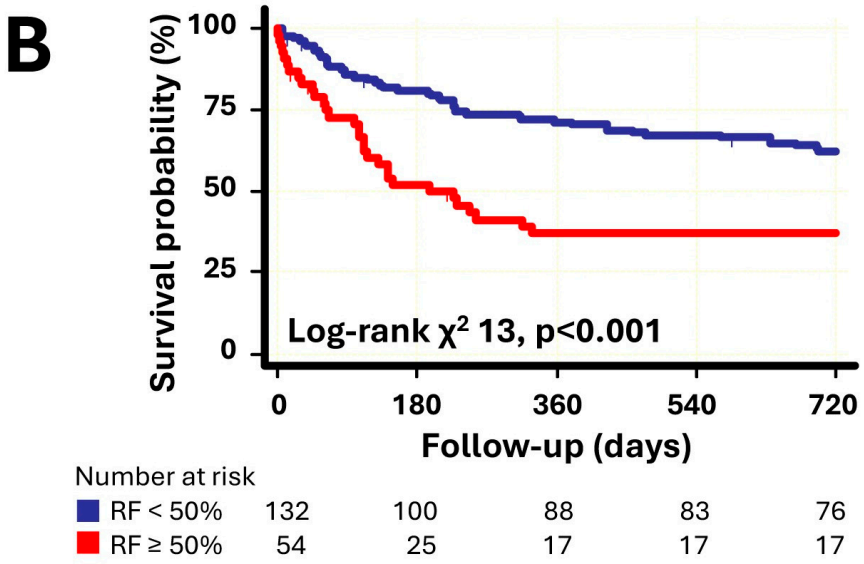

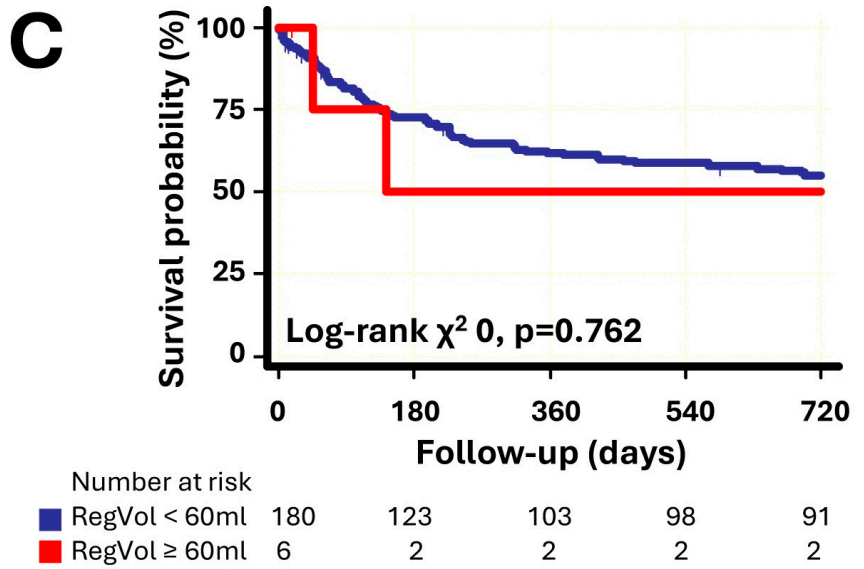

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Figure 2. Kaplan-Meier curve analysis of event-free survival according to parameters of MR severity: (A) EROA, (B) RF, (C) RegVol. Abbreviations as in Graphical abstract.

To assess the continuous association between quantitative parameters of MR severity and hazard ratio for clinical endpoint in our study cohort, spline curve analysis was performed. The risk for the composite endpoint began to increase at levels below the recommended cut-off for severe MR. Excess risk (HR > 1) was observed at around 20 mm² for EROA, 45% for RF and 30 ml for RegVol (**Figure 3**).

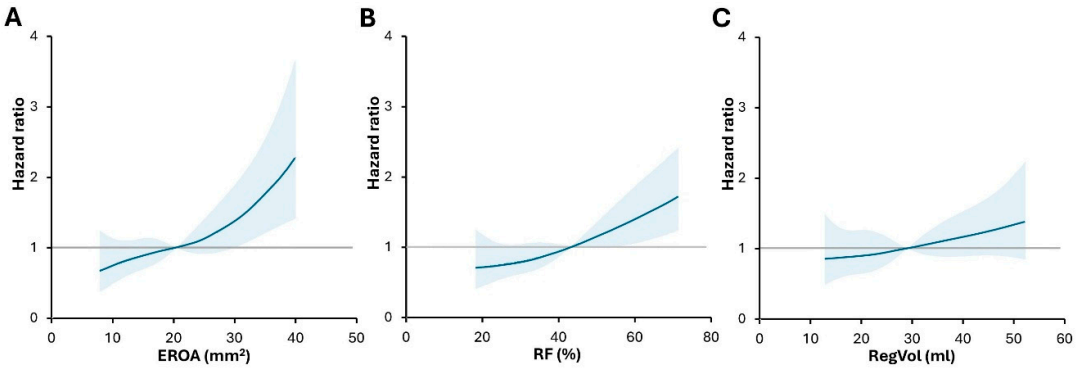

Figure 3. Spline curve showing the association between (A) EROA, (B) RF, (C) RegVol and outcome. The HR of 1 represents the mean risk of the study cohort. Solid blue line indicates HR, while the shaded area indicates 95% confidence interval. An excess risk for events (HR > 1) is observed at around 20 mm² for EROA, 45% for RF and 30 ml for RegVol. HR-hazard ratio, other abbreviations as in Graphical abstract.

The parameters associated with the composite endpoint in the univariate Cox regression analysis are presented in **Table 2**. In univariate analysis, EROA ≥ 40mm² and RF ≥ 50% were strongly associated with the composite endpoint, while RegVol ≥ 60 ml did not show significant association. In multivariable analysis, the association of EROA≥40mm², RegVol ≥ 60 ml and RF ≥ 50% with the composite endpoint was tested in addition to clinical and echocardiographic variables, including age, LVESV index, SV index, RV diameter and pulmonary systolic pressure (baseline model) (**Table 3**). Both EROA ≥ 40mm² and RF ≥ 50% were independently associated with increased HR for composite endpoint.

Using quantitative parameters of MR severity as continuous variables demonstrated similar results (**Tables S2-S3**).

Table 2. Univariate Cox regression analysis for the composite end point.

	HR (95% CI)	P-value
Age (years)	1.032 (1.016-1.050)	**<0.001**
Male sex	0.985 (0.655-1.450)	0.941
BMI (kg/m2)	0.962 (0.919-1.007)	0.099
Heart rate (bpm)	1.004 (0.996-1.013)	0.330
Atrial fibrillation (%)	1.236 (0.817-1.870	0.317
Ischemic cardiomyopathy (%)	1.183 (0.807-1.734)	0.389
LVEDD (mm)	1.004 (0.984-1.024)	0.706
LVESD (mm)	1.011 (0.994-1.029)	0.199
LVEDV index (ml)	1.004 (0.999-1.008)	0.098
LVESV index (ml)	1.007 (1.002-1.011)	**0.007**
LVEF (%)	0.967 (0.951-0.984)	**<0.001**
Stroke volume index (ml/m²)	0.976 (0.957-0.995)	**0.012**

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RV basal (mm)	1.768 (1.349-2.317)	**<0.001**
TAPSE (mm)	0.520 (0.338-0.800)	**0.003**
PASP (mmHg)	1.024 (1.009-1.039)	**0.001**
EROA (≥40mm²)	3.794 81.728-8.330)	**0.001**
RegVol (≥60ml)	0.806 (0.199-3.268)	0.762
RF (≥50%)	2.073 (1.385-3.103)	**<0.001**

Legend: abbreviation as in Table 1.

Table 3. Multivariable Cox regression models for the composite clinical endpoint.

	Model 1		**Model 2**		**Model 3**	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.036 (1.015-1.058)	**0.001**	1.041 (1.020-1.063)	**<0.001**	1.037 (1.016-1.059)	**0.001**
LVESV index (ml)	1.007 (1.001-1.012)	**0.016**	1.006 (1.000-1.011)	**0.049**	1.008 (1.002-1.013)	**0.006**
SV index (ml/m²)	0.975 (0.954-0.996)	**0.022**	0.976 (0.955-0.998)	**0.033**	0.978 (0.957-0.999)	**0.039**
RV basal (mm)	1.627 (1.197-2.212)	**0.002**	1.577 (1.158-2.147)	**0.004**	1.592 (1.184-2.142)	**0.002**
PASP (mmHg)	1.007 (0.990-1.025)	0.401	1.005 (0.988-1.022)	0.576	1.004 (0.987-1.021)	0.643
RegVol (≥60ml)	0.523 (0.121-2.255)	0.385				
EROA (≥40mm²)			2.811 (1.211-6.526)	**0.016**		
RF (≥50%)					1.757 (1.141-2.704)	**0.010**

Legend: abbreviation as in Table 1.

3.4. Added Value of Combining EROA and RF for the Composite Endpoint

As shown in **Figure 4**, adding either EROA ≥ 40mm² or RF ≥ 50% to the baseline model (age, LVESV index, SV index, RV diameter and pulmonary systolic pressure), improved the model and its association with clinical outcome. There was no significant difference in predictive value of the model containing EROA or RF (p=0.145). Furthermore, the model including both EROA and RF significantly outperformed models using either EROA ≥ 40mm² or RF ≥ 50% alone, demonstrating the increased prognostic value of combining EROA and RF to assess clinical outcome.

In the analysis, using MR severity parameters as continuous variables, the model with RF showed the strongest predictive value for composite outcome, while adding EROA to the model with RF, did not provide any further significant incremental value (**Figure S1**).

As EROA is typically used as a basic parameter to assess MR severity, we further evaluated risk stratification using RF in patient group with EROA < 40 mm² (**Graphical abstract**). Kaplan-Meier analysis showed that RF can be used for risk re-stratification in patients with EROA < 40 mm² (**Figure 5**). Patient subgroup with both EROA < 40mm² and RF < 50% had comparatively lower event rates for composite endpoints than patients with both EROA < 40mm² and RF ≥ 50% (log rank p = 0.002). In contrast, patient group with both EROA < 40mm² and RF ≥ 50% and group with EROA ≥ 40 mm² showed similar event rates (log rank p = 0.055).

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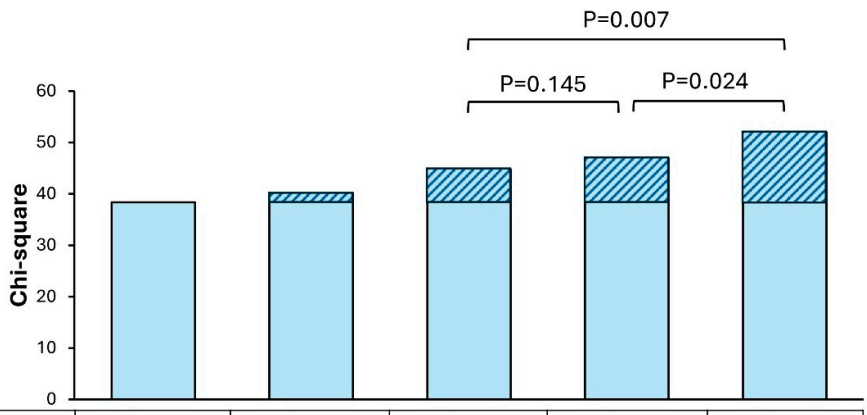

	Baseline model	Baseline model + RegVol≥60ml	Baseline model + RF≥50%	Baseline model + EROA≥40mm2	Baseline model + EROA≥40mm2 +RF≥50%
P-value for comparison with baseline model	-	0.185	0.011	0.003	0.001

Figure 4. Prognostic value of quantitative parameters of MR severity. Baseline model includes age, left ventricular end-systolic volume index, stroke volume index, right ventricular diameter and pulmonary systolic pressure. Models with RF ≥ 50% and EROA ≥ 40mm² were more accurate than baseline model in predicting risk of clinical endpoints, while there was no significant difference in prognostic power between them (p = 0.145). The model combining RF ≥ 50% and EROA ≥ 40mm² provides incremental prognostic value over models using single parameter of MR severity. The bar graphs show the chi-squares values for each model; the marked section of each bar indicates the change in chi-squares compared to the baseline model. Abbreviations as in Graphical abstract.

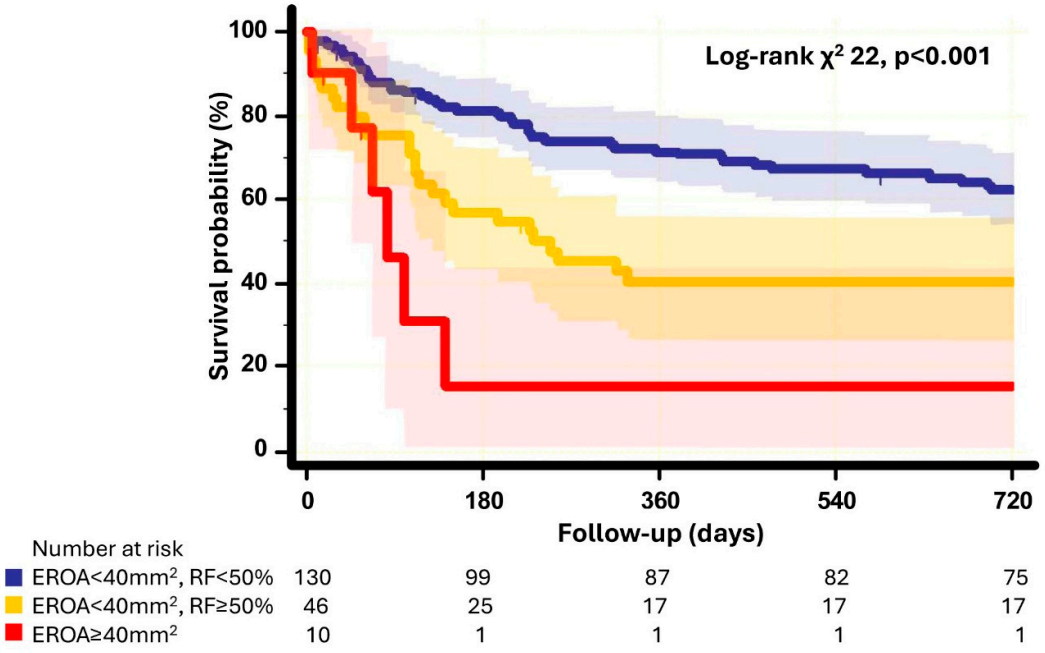

Figure 5. Kaplan-Meier curve analysis of event-free survival according to EROA and RF values. Comparison of survival between 3 patient subgroups: EROA ≥ 40mm² vs. EROA < 40mm²+RF ≥ 50% vs. EROA < 40mmm²+RF < 50%. Abbreviations as in Graphical abstract.

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4. Discussion

The key findings of our study exploring the prognostic value of quantitative parameters of MR severity in patients with ventricular secondary MR are as follows:

i) substantial discordance in MR grading was observed between EROA and RF, as well as between RegVol and RF,

ii) both EROA and RF were independently associated with clinical outcome, whereas no such association was found for RegVol,

iii) increased risk for composite endpoint was observed at lower thresholds of quantitative parameters than recommended cut-off values for severe ventricular secondary MR, and

iv) the combination of EROA, as a descriptor of lesion severity, and RF, as a descriptor of the haemodynamic significance of volume overload, provided incremental prognostic value over single parameters of MR severity. Importantly, RF demonstrated added value for further risk stratification in patients with non-severe MR according to EROA.

4.1. Concordance of Quantitative Parameters of MR Severity

Our results showed a good correlation between quantitative parameters of MR severity but marked discordance in the definition of severe MR between EROA and RF, and between RegVol and RF (in 26% and 27% of patients, respectively), whereas discordance between EROA and RegVol was relatively rare (4%). Previous studies have also found limited agreement on the quantitative parameters of MR severity [7,13,14]. Only 27% of patients in the predefined intermediate risk group had concordant parameters of EROA and RF [7]. Additionally, we showed that these discordances were more frequent in patients with smaller LV volumes and lower SV, consistent with the notion that EROA and RegVol are susceptible to underestimating the haemodynamic severity of MR in low flow conditions, as previously described [5,6].

Accurate assessment of the severity of MR remains challenging, particularly in the setting of underlying LV dysfunction, low-flow conditions and specific characteristics of the regurgitant orifice [9,10]. Grading MR severity using EROA or RegVol by PISA method may underestimate MR due to the crescent-shaped regurgitant orifice and the dynamic pattern of regurgitant flow [10,14–16]. Additionally, pressure gradients and orifice calculations are highly flow dependent. By contrast, RF considers the total volume of blood ejected by the LV and accounts for systemic flow. Therefore, EROA, RegVol and RF may show discordance in low or high flow states and may vary with LV size and function, as well as the pressure gradient between the LV and left atrium [6,10]. For example, RegVol of 30 ml and EROA of 20 mm^2 may be associated with RF ≥ 50% in a patient with reduced LVEF and reduced total LV stroke volume [6]. Therefore, RF could better identify patients with haemodynamically severe MR than EROA and RegVol (**Graphical abstract**). Accordingly, current guidelines [17–19] have recognised that the accepted thresholds for defining severe MR may be lower (EROA ≥ 30 mm^2), based on low-flow conditions and above mentioned PISA considerations. It is worth noting that the definition of low-flow state commonly used in the literature is based on an SV index < 35 ml/m^2 and has mainly been used to classify low-flow low-gradient aortic stenosis [20]. Current guidelines do not provide specific recommendations for defining or adjusting for low-flow states in MR [17–19]. Further studies are needed to determine which approach should be taken when measures of MR severity are discordant, and to better define haemodynamic states and echocardiographic characteristics when lower thresholds of EROA might be applicable.

4.2. Association of MR Grading with Clinical Outcome

The causal relationship between secondary MR and clinical outcome remains controversial [1,2,4,5,7,21–24]. Several studies have reported an association between parameters of MR severity and increased risk of adverse events in patients with reduced LVEF [2,3,5,7]. In our study, both EROA and RF were independently associated with adverse outcomes, reinforcing their individual prognostic value, whereas no significant association was found for RegVol. A unique finding of our

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study is that the combination of EROA and RF provided the highest predictive accuracy for the composite endpoint, suggesting that including both parameters improves risk stratification compared to either parameter alone. This supports the assertion that RF, as a flow-normalised parameter, may offer additional prognostic value, by reflecting haemodynamic burden of MR, in addition to the commonly used EROA.

Our results indicate that, in accordance with physiological concepts, it is important to consider both, the valve lesion and the haemodynamic significance of volume overload of MR. As previously mentioned, EROA and RegVol thresholds that define severe MR are related to LV volumes, LVEF and mean systolic pressure gradient between the LV and left atrium [6], while RF provides a normalised measure of RegVol to total stroke volume, enabling direct comparisons across patients with different LV sizes and haemodynamic states. This is particularly valuable in secondary MR, where the valve lesion, as assessed by EROA, can be within the range of moderate MR, but constitutes an RF > 50%, consistent with haemodynamically severe MR [6]. It appears that RF, while underutilised in everyday clinical practice, can provide a more objective measure of MR severity and may offer clinically meaningful benefit over other parameters of MR severity.

It is well recognised that an EROA≥40 mm^2 identifies patients with haemodynamically severe secondary MR and worse outcomes, while patients with EROA < 40mm^2 represent a highly heterogenous cohort with varying outcomes. Patients with discordant grading – EROA < 40 mm^2 and RF ≥ 50% – constituted a high-risk subgroup, as their survival rate was similar to that of patients with severe MR defined by EROA ≥ 40 mm^2. Our data corroborate previous study, which observed a threefold increase in mortality risk in the intermediate-risk subgroup of patients with non-severe MR (EROA 20–29 mm^2 and RegVol 30–44 ml) and with RF ≥ 50%, compared to patients with RF < 50% [7].

There is substantial data on specific thresholds of quantitative parameters associated with worse outcomes in secondary MR, with particular focus on EROA. Some data showed that categorical presence of secondary MR was associated with increased risk, but there was no linear increase in mortality risk with increasing EROA above zero [23], while another study demonstrated that the rate of excess mortality was stable up to EROA of 10 mm^2, then increased exponentially with rising EROA without plateau [5]. Our spline curve analysis showed a continuous increase in risk with increasing MR severity parameters, with an excess of adverse events (HR > 1) at around EROA 20 mm^2, RegVol 30 ml and RF 45%. Other authors have also demonstrated that the risk begins to increase at EROA or RegVol levels below the guideline recommended cut-offs for severe MR [3–5,7]. Studies have reported different thresholds at which significantly higher risk occur, ranging from 10 mm^2 to 30 mm^2 for EROA and 30 ml to 60 ml for RegVol. The diversity of reported thresholds might be due to heterogeneous study cohorts, including both entities of secondary MR – atrial [4,23] and ventricular MR [3,5,7] – as well as a broad spectrum of LV size and systolic function. This highlights the potential limitation of a uniform threshold for EROA and RegVol, given their important, yet often underappreciated dependence on LV pressure, volume and LVEF [6,25]. Conversely, outcome data regarding specific RF thresholds in secondary MR are lacking [4,7]. Similar to our results, studies identify a threshold for significantly higher risk at around RF 50%, despite very diverse study cohorts. In contrast to EROA and RegVol, the prognostic value of RF aligns perfectly with the guideline definition of severe MR. These results once again raise intriguing debate about whether we should base the criteria for quantifying ventricular secondary MR on prognostic information.

4.3. Clinical Implications

The main finding of our study is the incremental value of RF in refining risk stratification and guiding more individualised clinical decisions, especially when quantitative parameters are discordant. The combination of EROA as a descriptor of lesion severity and RF as a descriptor of the haemodynamic burden of MR, may provide the best prediction of outcome and as such may be a valuable clinical tool in decision making.

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Our data support a greater emphasis on quantitative metrics, especially RF, when predicting patient outcomes. Additionally, it should be recognised that an EROA < 40 mm² does not necessarily imply a favourable prognosis, and that flow conditions, LV size and function, as well as haemodynamic significance of volume overload as assessed by RF, should be considered.

Therefore, we suggest that RF could be incorporated into clinical practice to improve the assessment and risk stratification of ventricular secondary MR (**Graphical abstract**). This is particularly relevant in low-flow states, rendering absolute values of EROA and RegVol less reliable indicators of MR severity. In this context, RF expressed as a percentage of total SV, provides a more robust index of regurgitant burden and showed consistent prognostic value in the analytic model. However, it remains to be demonstrated whether this concept can improve patient selection for valve interventions and consequently reduce mortality and heart failure hospitalisation.

4.4. Limitations

Our study is retrospective and single-centre with a relatively small number of patients, which may limit its generalisability. The population was restricted to ventricular secondary MR, so the results may not apply to primary MR or atrial secondary MR. Some patients in our study group might have dual functional MR. However, according to our inclusion criteria, patients primarily met the criteria for ventricular MR, meaning that the atrial component could not be the leading mechanism of MR.

The use of single-frame mid-systolic PISA measurements, although consistent with recommendations, may underestimate the severity of regurgitation in dynamic MR. Additionally, we used Simpson's method instead of the Doppler method with inflow VTI at the mitral annulus to assess total SV. The Doppler method uses a greater number of potential variables, such as mitral annulus geometry, sample volume position and angulation, that can affect the precision of the SV calculation compared to the Simpson`s method. SV measured by the Simpson`s method is an accurate measurement, which showed a good correlation with similar measurements by cardiac magnetic resonance (CMR) [26].

Finally, advanced imaging modalities such as 3D echocardiography (e.g. 3D vena contracta area) or CMR might provide more robust quantification and risk stratification in future studies. A recent study has already demonstrated that EROA measured by 3D echocardiographic volumetric method improves risk stratification in patients with ventricular MR compared to standard PISA method [3].

5. Conclusions

Our study highlights the challenges and new insights associated with quantifying ventricular secondary MR. Substantial discordance between quantitative parameters of severe MR was frequently observed in ventricular secondary MR in routine clinical practice. Increased risk of adverse events appeared at EROA of around 20mm² with continuous increase as EROA increased. The subset of patients with an EROA < 40mm² and an RF > 50% had a prognosis comparable to those who met the guideline-based threshold for severe MR, defined as EROA ≥ 40mm². These findings underscore the clinical value of routinely assessing RF to refine risk stratification and identify high-risk subgroup of patients with EROA < 40 mm². Integrating RF assessment could enhance diagnostic precision and risk stratification in patients with ventricular secondary MR. Further studies are needed to validate these findings and explore their integration into clinical decision-making for patients with ventricular secondary MR.

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Supplementary Materials: The following supporting information can be downloaded at: …….., **Supplemental Table S1:** Characteristics of the study group with concordant grading of MR and study group with discordant grading of MR; **Supplemental Table S2:** Univariate Cox regression analysis for the composite end point; **Supplemental Table S3:** Multivariable Cox regression models for the composite clinical endpoint; **Supplemental Figure S1:** Prognostic value of quantitative parameters of MR severity, as a continuous variable.

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